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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 473/00, A61K 31/52 — A1

(11) International Publication Number: **WO 96/02543**

(43) International Publication Date: 1 February 1996 (01.02.96)

(21) International Application Number: PCT/EP95/02705

(22) International Filing Date: 12 July 1995 (12.07.95)

(30) Priority Data:
9414208.0 14 July 1994 (14.07.94) GB

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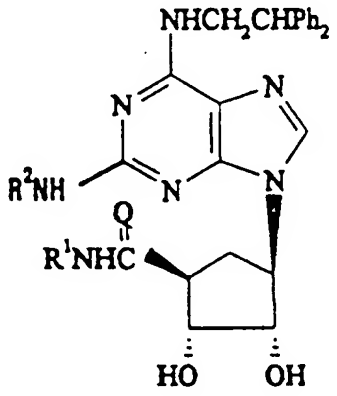
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 2,3-DIHYDROXY CYCLOPENTANE DERIVATIVES OF PURINES

(57) Abstract

2,3-dihydroxy cyclopentane derivatives are described having general formula (I) and salts and solvates thereof, wherein: R^1 is hydrogen, C_{3-8}cycloalkyl or C_{1-6}alkyl; R^2 is C_{3-8} cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, Alk_1Y, $-(CHR^5)_m(Alk_2)_nZ$ or appropriately substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl, and Q is oxygen or sulphur. Compounds of formula (I) and their salts and solvates have use in medicine as anti-inflammatory agents, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.



(I)

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2,3-DIHYDROXY CYCLOPENTANE DERIVATIVES OF PURINES

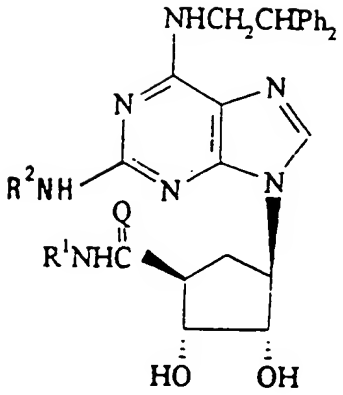
The present invention relates to therapeutically active substituted 2,3-dihydroxy cyclopentane derivatives, processes for the manufacture of said compounds, pharmaceutical formulations containing said compounds and the use of said compounds in chemotherapy. In particular, we have found a group of novel compounds which are effective in treating inflammatory diseases.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by circulating leukocytes binding to and extravasion through vascular endothelium. Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by gene expression in vascular endothelium in response to a variety of inflammatory mediators.

The primary function of leukocytes is to defend the host from invading organisms such as bacteria and parasites. Once a tissue is injured or infected a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment and resolution are not adequately controlled and the inflammatory reaction causes tissue destruction.

We have now found a novel group of compounds with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation. The compounds are therefore of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation. The compounds of the invention may also represent a safer alternative to corticosteroids in the treatment of inflammatory diseases, whose uses are severely limited by their side-effect profiles.

Thus, according to one aspect of this invention, we provide a compound of general formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-8}cycloalkyl or C_{1-6}alkyl group;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

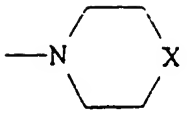
(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) $-Alk_1Y$ where Alk_1 is a C_{2-6} alkylene group and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl) and

(viii) $-(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, carboxyC_{1-4}alkyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts such as acid addition salts derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates and maleates, and, if appropriate, inorganic base salts such as alkali metal salts, for example sodium salts. Other salts of the compounds of formula (I) include salts which are not physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. Examples of such salts include trifluoroacetates.

Examples of suitable solvates of the compounds of formula (I) include hydrates.

It will be appreciated that when R^2 in compounds of formula (I) contains one or more asymmetric carbon atoms the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. Otherwise, the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

It is to be understood that all tautomeric forms of the compounds of formula (I) are included within the scope of this invention.

The cycloalkyl group within R^1 or R^2 may be a monocyclic or bridged cyclic ring. Particular examples of suitable cycloalkyl ring systems include C_{3-8} monocyclic cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl. Within R^2 the C_{3-8} cycloalkyl group may particularly represent cyclopentyl or cyclohexyl.

The term 'aryl' as part of an arylC_{1-6}alkyl group may represent, for example, a phenyl group optionally substituted by one or more substituents (e.g. 1, 2 or 3 substituents) which may be the same or different and are selected from halogen, hydroxyl, C_{1-3}alkoxy and C_{1-3}alkyl.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group. Particular examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl.

The term 'alkylene' as part of a group means a straight or branched alkylene chain. Particular examples of suitable alkylene chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CHCH_3CH_2-$ and $-CH_2C(CH_3)_2CH_2-$.

When R^2 represents a group $-Alk_1Y$ the C_{2-6}alkylene group may particularly represent $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2C(CH_3)_2CH_2-$.

When R^2 represents a group $-(CHR^5)_m(Alk_2)_nZ$ the chain $-(CHR^5)_m(Alk_2)_n-$ may particularly represent a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^5CHCH_3CH_2-$ or $-CHR^5CH_2-$ (where R^5 is a group CH_2R^6 and R^6 is as defined previously).

The term 'C_{2-7}acylamino' within R^2 means a C_{2-7}alkanoylamino group wherein the C_{1-6}alkyl portion thereof is a straight or branched alkyl group as previously defined and may be optionally substituted by one or more halogen atoms such as fluorine. Examples of suitable C_{2-7}alkanoylamino groups within R^2 include acetamido and trifluoroacetamido.

Within Z, the term 'pyridyl' means a 2-, 3- or 4-pyridyl group; the term 'pyrimidinyl' means a 2-, 4- or 5-pyrimidinyl group; the term 'imidazolyl' means a 1-,2-,4- or 5-imidazolyl group; and the term 'triazolyl' means a 1, 2, 4-triazolyl group (e.g. 1, 2, 4-triazol-l-yl or 1, 2, 4-triazol-3-yl).

R^1 preferably represents a C_{1-3}alkyl group, especially ethyl.

Compounds of formula (I) in which Q represents an oxygen atom are generally preferred.

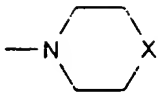
Compounds of formula (I) in which $R^1NHC(=Q)$- represents ethylaminocarbonyl are particularly preferred.

A preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a substituted cyclopentyl or cyclohexyl group wherein the ring is substituted by one or two groups, especially one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido. Preferred substituents include hydroxy, NH_2 and dimethylamino.

A further preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a pyrrolidin-3-yl or piperidin-3-yl group in which the ring nitrogen atom is substituted by hydrogen, C_{1-3}alkyl (e.g. ethyl) or benzyl.

Another preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents $(CHR^5)_m(Alk_2)_nZ$ where R^5, m and n are as defined previously and Z is an optionally substituted imidazolyl group. Particularly preferred are those compounds in which $-(CH_2R^5)_m(Alk_2)_n-$ represents $-CH_2CH_2-$.

Yet a further preferred group of compounds of the invention are compounds of formula (I) in which R^2 is Alk_1Y where Alk_1 is a C_2alkylene group and Y is



(where X is a bond, O, CH_2).

It is to be understood that the present invention covers all combinations of particular and preferred groups referred to hereinabove.

Specific compounds of the present invention include:
(1S,2R,3S,4R)-4-[trans-2-(4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide;
(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(piperidin-1-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide;
(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide; and

and physiologically acceptable salts and solvates thereof.

The potential for compounds of formula (I) to inhibit leukocyte function may be demonstrated, for example, by their ability to inhibit superoxide (O_2^-) generation from neutrophils stimulated with chemoattractants such as N-formylmethionyl-leucyl-phenylalanine (fMLP). Accordingly, compounds of formula (I) are of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, asthma (including allergen-induced asthmatic reactions), emphysema, rhinitis and septic shock. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease

(e.g. Crohn's disease or ulcerative colitis), Helicobacter-pylori induced gastritis and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, and non-steroidal anti-inflammatory drug-induced gastropathy. Furthermore, compounds of the invention may be used to treat skin diseases such as psoriasis, allergic dermatitis and hypersensitivity reactions.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiac conditions such as peripheral vascular disease, post-ischaemic reperfusion injury and idiopathic hypereosinophilic syndrome.

Compounds of the invention which inhibit lymphocyte function also have use in the treatment of auto-immune diseases such as rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with

inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition who is susceptible to leukocyte-induced tissue damage, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable carriers or excipients.

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration, preferably for parenteral or topical (e.g. by aerosol) administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats;

emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator, solutions for nebulisation or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such

as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges of for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents such as corticosteroids or NSAIDs.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example an anti-inflammatory agent such as a corticosteroid or NSAID.

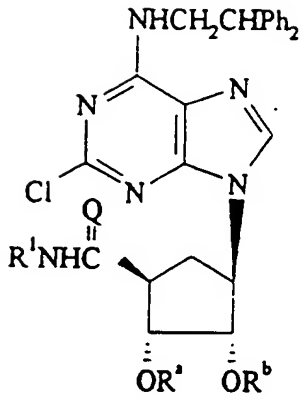
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.01 to 500mg/kg body weight, preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention. In the following procedures, the groups R^1, R^2 and Q are as defined for compounds of formula (I) unless otherwise stated.

Thus, according to first process (A), a compound of formula (I) may be prepared by treating a compound of formula (II)



(II)

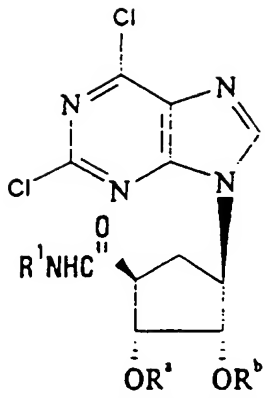
(wherein R^a and R^b each represent a hydrogen atom or together form an alkylidene group such as isopropylidene) with an amine $R^{2a}NH_2$ (wherein R^{2a} is a group R^2 or is a protected derivative thereof), followed, where necessary, by the removal of any protecting groups present.

The displacement reaction to introduce the amine moiety may be carried out by heating the reagents at a temperature in the range of 50^0 to 150^0C optionally in the presence of a solvent such as dimethylsulphoxide.

A compound of formula (II) in which Q represents a sulphur atom may be prepared from a compound of formula (II) in which Q represents an oxygen atom and R^a and R^b together form an alkylidene group such as isopropylidene by thianation followed, if appropriate, by the removal of the alkylidene group.

The thianation reaction may be conveniently effected using known thianation agents such as hydrogen sulphide, phosphorus pentasulphide or Lawesson's reagent (p-methoxyphenylthiophosphine sulphide dimer). The reaction may be carried out in a known manner. For example when hydrogen sulphide is used an acid such as hydrochloric acid may conveniently be added in catalytic amounts and the reaction carried out in a polar solvent such as acetic acid or ethanol. When using Lawesson's reagent, the reaction may conveniently be carried out in a dry solvent such as toluene or methylene chloride.

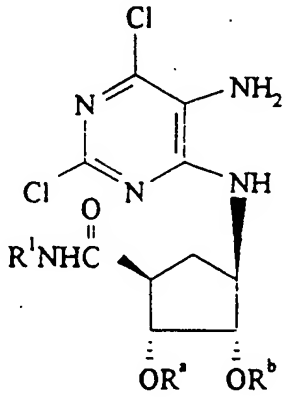
A compound of formula (II) in which Q represents an oxygen atom may be prepared by treating a compound of formula (III)



(III)

(wherein R^a and R^b are as defined previously) with 2,2-diphenylethylamine, preferably in the presence of a base such as an amine base (e.g. diisopropylethylamine) and in a solvent such as an alcohol (e.g. isopropanol) at an elevated temperature (e.g. reflux), followed if desired by removing any protecting groups present.

Compounds of formula (III) may be obtained from intermediates of formula (IV)



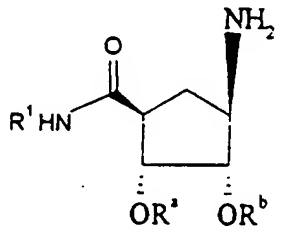
(IV)

(wherein R^1, R^a and R^b are as previously defined) by reaction with a compound of formula $(R^cO)_3$ CH (where R^c represents C_{1-4}alkyl) under acidic conditions, followed by heating at, for example, about 100-120°C, followed if desired by removing any protecting groups present.

Alternatively, compounds of formula (II) may be prepared from compounds of formula (IV) by reaction with a compound of formula $(R^cO)_2CHO_2CR^d$ (where R^c and R^d each independently represents C_{1-4}alkyl) followed by reaction with

2,2-diphenylethylamine, preferably in the presence of a base as previously described followed if desired by removing any protecting groups present.

Compounds of formula (IV) may be prepared by reaction of compounds of formula (V)

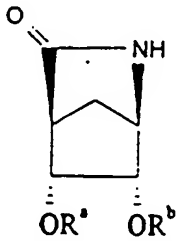


(V)

(wherein R^1, R^a and R^b are as previously defined) with 5-amino-2,4,6-trichloropyrimidine in the presence of a base.

Suitable bases for use in the reaction include tertiary amines such as, for example, triethylamine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, butanol, preferably at elevated temperature, such as the reflux temperature of the chosen solvent.

Compounds of formula (V) may be prepared by any of the methods known in the art for the preparation of compounds of analogous structure. For example, according to one method, compounds of formula (V) may be prepared from intermediates of formula (VI)

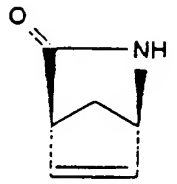


(VI)

by reaction with an amine of formula R^1NH_2 at elevated temperature and pressure.

The reaction is suitably conducted in a bomb heated to about 150-160°C.

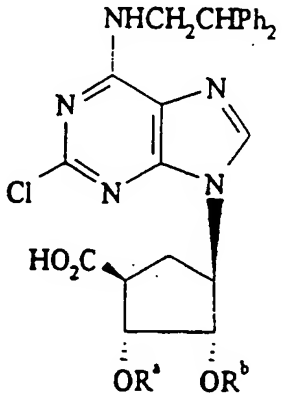
Compounds of formula (VI) may be prepared by hydroxylation of the known compound of formula (VII)



(VII)

followed by introduction of protecting groups R^a and R^b, if required.

A compound of formula (II) in which Q represents an oxygen atom may also be prepared by treating a compound of formula (VIII)

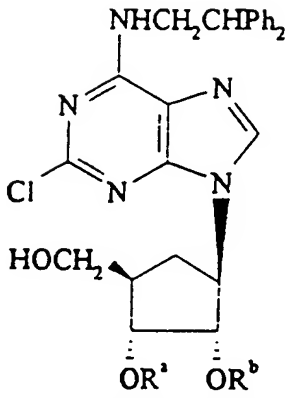


(VIII)

(wherein R^a and R^b are as defined previously) or an active derivative thereof such as a corresponding mixed anhydride with an amine R^1NH_2, followed if desired by removing any protecting groups present.

The amination reaction may be effected in known manner, for example by adding the amine in a solvent such as a halogenated hydrocarbon (e.g. methylene chloride) or in dimethylformamide, in the presence of an amine such as triethylamine at about 0° to 20°C to the compound (VIII) or, more particularly, a corresponding mixed anhydride. The mixed anhydride may be prepared, for example, by treating compound (VIII) with pivaloyl chloride, conveniently at about 0°C.

A compound of formula (VIII) may be prepared by oxidising a compound of formula (IX)

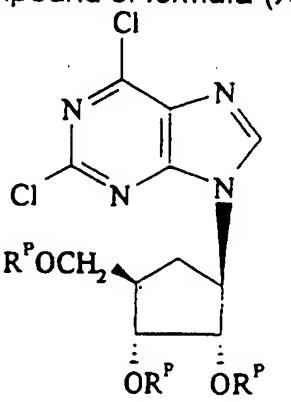


(IX)

or a salt thereof (wherein R^a and R^b together form an alkylidene group such as isopropylidene), followed if desired by removing the alkylidene group. The oxidation reaction may be effected in known manner using an oxidising agent such as potassium permanganate or pyridinium dichromate, or, preferably, ruthenium trichloride in the presence of sodium periodate .

Compounds of formula (IX) wherein R^a and R^b represent an alkylidene group may be prepared from the corresponding compounds of formula (IX) wherein R^a and R^b each represent H by conventional methods.

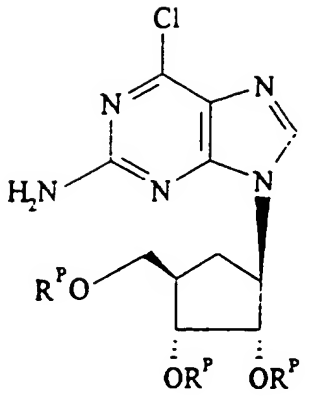
A compound of formula (IX) wherein R^a and R^b each represents H may be prepared by treating a compound of formula (X)



(X)

(wherein R^P is a suitable hydroxyl protecting group, such as an acyl group) with 2,2-diphenylethylamine under the conditions described previously for preparing compounds of formula (II) from compounds of formula (III), followed by removal of the protecting groups R^P in conventional manner.

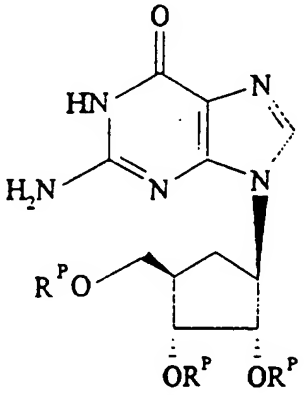
Compounds of formula (X) may be prepared from compounds of formula (XI)



(XI)

by reaction with a suitable chlorinating agent, such as pyridine hydrochloride in the presence of copper (I) chloride and t-butyl nitrite.

Compounds of formula (XI) may be prepared from compounds of formula (XII)



(XII)

by reaction with phosphorous oxychloride under conventional conditions.

Compounds of formula (XII) are known compounds or may be prepared from known compounds by conventional procedures readily appreciated by those skilled in the art.

The amines $R^{2a}NH_2$ are either known in the art or may be prepared by the methods described in the Examples Section hereinafter or by methods analogous to such methods hereinafter.

Compounds of formulae (II), (VIII), (IX) and (X), are novel intermediates and represent further aspects of the present invention. Compounds of formula (II) in which R^a and R^b represent hydrogen atoms are also active compounds in their own right and constitute a further particular aspect of the present invention.

It will be appreciated that in addition to 2,3-diol groups, groups present within R^2 may need to be protected, and deprotection may be required as an intermediate or final step to yield the desired compound. Thus, according to another general process (B), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) or sulphonyl (e.g. allylsulphonyl or tosyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene and P.G.M. Wuts (John Wiley and Sons, 1991). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride. Carboxyl protecting groups may conveniently be represented by appropriate hydroxyl

protecting groups above with deprotection effected according to the methods described above. An example of such a group is an alkyl (e.g. methyl or t-butyl) group which can be removed by acid hydrolysis (e.g. using trifluoroacetic or hydrochloric acid) or an aralkyl (e.g. benzyl) group which can be removed by catalytic hydrogenolysis.

Particularly suitable hydroxyl protecting groups represented by R^P include acyl groups such as acetyl or benzoyl. An alkylidene protecting group may conveniently be removed by acid-catalysed hydrolysis, for example using trifluoroacetic, sulphuric or hydrochloric acid.

Compounds of formula (I) may also be prepared from other compounds of formula (I) or protected derivatives thereof using conventional interconversion procedures, including N-acylation, N-debenzylation and oxidation of a hydroxyl group to a ketone, followed, if necessary, by the removal of any protecting groups present.

Individual isomers of formula (I) may either be prepared from starting materials having the desired stereochemistry or by epimerisation, resolution or chromatography (e.g. HPLC separation) at an appropriate stage in the synthesis of the required compounds of formula (I) as appropriate using conventional means.

When it is desired to prepare an acid addition salt of a compound of formula (I) the product of the above procedure may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) in the form of a free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol, ethanol or isopropanol).

Inorganic basic salts may be prepared by reacting a compound of formula (I) using conventional methods.

Solvates (e.g. hydrates) of a compound of formula (I) may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Hereinafter the term DMSO means dimethylsulphoxide. IMS means industrial methylated spirit.

EXAMPLES

General

Where products were purified by column chromatography, 'silica' refers to silica gel for chromatography, 0.063 to 0.20mm mesh (e.g. Merck Art 7735); 'flash silica' refers to silica gel for chromatography, 0.040 to 0.063mm mesh (e.g. Merck Art 9385). In this latter case column elution was accelerated by an applied pressure of nitrogen at up to 10 p.s.i

Intermediate 1

(1R, 4S, 5R, 6S)-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptan-3-one

To a stirred solution of N-methylmorpholine N-oxide (126.7g) in water (390ml) was added a solution of osmium tetroxide (0.5% w/v in *t*-butanol; 167ml) and a suspension of (1R, 4S)-2-azabicyclo[2.2.1]hept-5-en-3-one[1] (100g) in *t*-butanol (500ml). The reaction was heated at 70°C for 30 min, then cooled to 50°C. Sodium dithionite was added and the reaction further cooled to 30°C. Charcoal (Norit Ultra SX+, 40g) was added and stirring continued for 30min. The insolubles were removed by filtration and the filtrate concentrated under vacuum. The residue was refluxed in IMS (1 l) and the inorganic insolubles removed by filtration and the filtrate concentrated to 400ml, heated to reflux then allowed to cool. Filtration afforded the title compound as fawn crystals (112.7g). m.p. 165.5°C; $[\alpha]_D^{21}$ = -94.9° (c = 1.20, H_2O); ^{1}H nmr δ (DMSO-d_6) 1.72 (dd, 1H), 1.90 (dd, 1H), 2.26 (s, 1H), 3.43 (s, 1H), 3.74 (m, 2H), 4.99 (dd, 2H), 7.53 (br s, 1H).

1. SJC Taylor, R McCague, R Wisdom, C Lee, K Dickson, G Ruecroft, F O'Brian, J Littlechild, J Bevan, SM Roberts and TC Evans, *Tetrahedron Asymmetry*, **1993**, *4*, 1117.

Intermediate 2

(1S.2R,6S,7R)-4,4-Dimethyl-3,5-dioxa-8-azatricyclo [5.2.1.0.2,6] decan-9-one

A suspension of (1R, 4S, 5R, 6S)-5-6-dihydroxy-2-azabicyclo [2.2.1] heptan-3-one (10g) in 2,2-dimethoxypropane (200ml) and dimethyl formamide (100ml) was treated with p-toluene sulphonic acid monohydrate (640mg). It was stirred at room temperature for 24h. The reaction mixture was reduced in volume by evaporation *in vacuo* and the residue was triturated with a small amount of ethyl acetate to give the title compound (5.078g) as a white solid which as collected by filtration.

The mother liquors were evaporated to give a solid residue which was purified by column chromatography on flash silica eluted with methanol-chloroform mixture (0% → 15%) to give more of the title compound (6.696g) as a white solid. ^{1}H nmr δ ($CDCl_3$) 1.36 (s, 3H), 1.47 (s, 3H), 2.1 (m, 2H), 2.74 (s,1H), 3.80 (s, 1H), 4.42 (d, 1H), 4.56 (d, 1H), 5.99 (s,1H).

Intermediate 3

(3aR,4S,6R,6aS)-6-Amino-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid ethylamide

(1S,2R,6S,7R)-4,4-Dimethyl-3,5-dioxa-8-azatricyclo [5.2.1.0. .2,6] decan-9-one (22.901g) was treated with neat ethylamine (140ml) in a Hast-C-alloy bomb. It was heated in an oil bath at 159°C for 17h. (The bomb pressure gauge reading was 250 p.s.i) After allowing it to cool down, the pressure was released and the mixture was evaporated to give an oily residue. It was purified by column chromatography on flash silica eluted with methanol chloroform mixture (15% → 50%) to give the title compound (21.34g) as a brown gum. ^{1}H nmr δ ($CDCl_3$) 1.14 (t, 3H), 1.31 (s, 3H), 1.46 (s, 3H), 1.7-2.5 (m. 2H), 2.77 (m, 1H), 3.27 (m, 2H), 3.5 (m, 1H), 4.38 (d, 1H), 4.83 (m, 1H), 6.60 (s, 1H).

Alternative method for the preparation of Intermediates 2 and 3

A solution of ethylamine (50ml) in dichloromethane (420ml) was stirred under nitrogen and treated dropwise with a solution of trimethyl aluminium (2M) in toluene (85ml). It was stirred at room temperature under nitrogen to give a solution of dimethyl aluminium ethyl amide.

(3aR,4S,6R,6aS)-6-Amino-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid methyl ester hydrochloride (21.21g) as a solid under nitrogen was treated dropwise with the stock solution of dimethylaluminium ethylamide in dichloromethane (260 ml). It was stirred at room temperature under nitrogen for 4hrs and then carefully quenched with water. The mixture was diluted with water (400ml) and extracted with ethyl acetate (1.25l x 2). The organic extract was dried over magnesium sulphate and the solvent was evaporated to give a solid residue (10.121g). This residue was chromatographed on flash silica, eluted with methanol chloroform mixture (10%→ 50%) to give (1S, 2R, 6S, 7R)-4-4-dimethyl-3,5,dioxa-8-aza-tricyclo [5.2.1.0. 2,6] decan-9-one as a white solid (6.29g) whose ^{1}H nmr spectrum ($CDCl_3$) was identical to that of the authentic sample (vide supra) and (3aR,4S,6R,6aS)-6-amino-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide as a gum (4.611g) whose ^{1}H nmr spectrum ($CDCl_3$) was identical to that of the authentic sample (vide supra).

Intermediate 4

(1S, 2R, 3S, 4R)-4-Amino-2,3-dihydroxycyclopentanecarboxylic acid methyl ester, hydrochloride

A solution of (1R, 4S)-2-azabicyclo[2.2.1]hept-5-en-3-one[1] (112.3g) in 3M hydrochloric acid (800ml) was refluxed for 1h. The reaction was concentrated under vacuum and the residue evaporated with methanol (800ml) then toluene (3 x 250ml). The resulting solid was dissolved in 1M methanolic HCl (800ml) and refluxed for 1h. The solvent was removed under vacuum and 2-propanol was added. The resulting slurry was stirred at 0°C for 45min and the title compound isolated by filtration as a light grey solid (147.7g). m.p. 159.8°C; $[\alpha]_D^{25}$ -14.9° (c = 1.40, H_2O); $_1$H nmr δ (D_2O) 1.86 (m, 1H), 2.54 (m, 1H), 3.01 (m. 1H), 3.60 (q, 1H), 3.77 (s, 3H), 4.10 (t, 1H), 4.31 (t, 1H).

1. SJC Taylor, R McCague, R Wisdom, C Lee, K Dickson, G Ruecroft, F O'Brian, J Littlechild, J Bevan, SM Roberts and TC Evans, *Tetrahedron Asymmetry*, **1993**, *4*, 1117.

Intermediate 5

(3aR,4S,6R,6aS)-6-Amino-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid methyl ester hydrochloride salt

A stirred suspension of (1S,2R,3S,4R)-4-Amino-2,3-dihydroxy-cyclopentanecarboxylic acid methyl ester hydrochloride (50g, 0.2362 mole), p-toluene sulphonic acid monohydrate (2g) in 2,2-dimethoxypropane (500ml) and N,N-dimethyl formamide (400ml) was stirred at room temperature for 24h. (It became a clear solution by 2h and again a suspension by 24h). The precipitate was collected by filtration, washed with a small quantity of ethyl acetate to give the title compound (7.95g) as a white solid. The filtrate was evaporated to dryness and the residue was triturated with ethyl acetate to give more of the title compound (47.52g) as a white solid. ^{1}H nmr δ (D_2O) 1.36 (s, 1H). 1.53 (s,1H), 2.12 (m, 1H), 2.61 (m,1H), 3.20 (m, 1H), 3.76 (m, 1H), 3.76 (s, 1H), 4.78 (m, 1H), 4.99 (m, 1H).

Intermediate 6

(3aR,4S,6R,6aS)-6-(5-Amino-2,6-dichloro-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide

5-Amino-2,4,6-trichloropyrimidine (500mg) was treated with a solution of (3aR,4S,6R,6aS)-6-amino-2,2-dimethyl-tetrahydro-cyclopenta [1,3]dioxole-4-carboxylic acid ethylamide (581 mg) in butan-1-ol (26 ml) and triethylamine (3.5ml). The reaction mixture was heated under reflux under nitrogen for 22h. It was allowed to cool and the solvent was removed under reduced pressure to give a residue (1.886g). This residue was purified by column chromatography on flash silica, eluted with ethyl acetate-cyclohexane mixtures (33% → 75%) to give the title compound as a foam (742mg) MH+ measured at 390.109909 $C_{15}H_{22}Cl_2N_5O_3$ requires 390.109970, ^{1}H nmr δ ($CDCl_3$) 1.18 (t, 3H), 1.28 (s, 1H). 1.46 (s, 1H), 1.85-2.67 (m,2H) 2.85 (d, 1H), 3.32 (m,2 H), 3.66 (s, 2H), 4.52 (d, 1H), 4.75 (t, 2H), 5.94 (s, 1H), 8.06 (d, 1H).

Intermediate 7

(3aR,4S,6R,6aS)-6-(2,6-Dichloro-5-methoxymethyleneamino-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide

Trimethyl orthoformate (4ml) and concentrated hydrochloric acid (0.05ml) were added to (3aR, 4S, 6R, 6aS)-6-(5-Amino-2,6-dichloro-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide (250mg). The reaction mixture was stirred at room temperature for 2h and then the solvent removed under reduced pressure to give a gum (352 mg). It was purified on flash silica, eluted with ethyl acetate-cyclohexane mixtures (20% → 50%) to give the title compound as a white foam (161mg,). MH^+ measured at 432.120908 C_{17} H_{24} Cl_2 N_5 O_4 requires 432.120535; ^1H nmr δ ($CDCl_3$) 1.15 (t, 3H), 1.27 (s, 3H), 1.47 (s, 3H), 1.80 - 2.60 (m, 2H), 2.80 (d, 1H), 3.26 (m, 2H), 4.11 (s, 3H), 4.49 (d, 1H), 4.75 (m, 2H), 5.79 (s, 1H), 7.86 (s, 1H), 8.09 (d, 1H).

Intermediate 8

(3aR,4S,6R,6aS)-6-(2,6-Dichloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3] dioxole-4-carboxylic acid ethylamide

A stirred solution of (3aR,4S,6R,6aS)-6-(2,6-Dichloro-5-methoxymethyleneamino-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid ethylamide (560mg) in butan-1-ol (15ml) was heated under reflux for 4h. It was allowed to cool and the solvent was evaporated under reduced pressure to give an oily residue (637mg). This residue was purified by column chromatography on flash silica, eluted first with ethyl acetate-cyclohexane mixtures (25% → 83%) then with 10% methanol in chloroform to give the title compound as a gum (46mg). MH^+ measured at 400.09422 C_{16} H_{20} Cl_2 N_5 O_3 requires 400.094320; ^1H nmr δ ($CDCl_3$) 1.18 (t, 3H), 1.23 (s, 3H), 1.59 (s 3H) 2.68 (m, 2H), 2.86 (m, 1H), 3.35 (m, 2H), 4.96 (m. 3H) 5.77 (t, 1H), 8.32 (s, 1H).

Alternative Preparation of Intermediate 8.

Triethylorthoformate (8ml) and concentrated hydrochloric acid (0.1ml) was added to (3aR,4S,6R,6aS)-6-(5-Amino-2,6-dichloro-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide (500 mg). The reaction mixture was stirred at room temperature for 24h and then

the solvent was evaporated under reduced pressure to give a gum. This gum was treated with butan-l-ol (15ml) and heated under reflux under nitrogen for 4 days. It was allowed to cool and the solvent was evaporated under reduced pressure to give a brown foam (576mg). This was purified by column chromatography on flash silica eluted with methanol-chloroform mixtures (0% → 5%) to give (3aR, 4S,6R, 6aS)-6-(2,6-Dichloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole -4-carboxylic acid ethylamide as a gum (87mg) which was identified on t.l.c. to the authentic material described above, and a more polar product (1S,2R,3S,4R)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide (Intermediate 11) as a gum (122mg).

Intermediate 9

(3aR,4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid ethylamide

(3aR,4S,6R,6aS)-6-(5-Amino-2,6-dichloro-pyrimidin-4-yl-amino)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid ethylamide (12.21g) in diethoxymethyl acetate (240ml) was heated at reflux, under nitrogen, for 2 days. A futher addition of diethoxymethyl acetate (75ml) was made and the heating was continued for a further 24h. The solvent was evaporated under reduced pressure to give a brown gum (17.62g) which was chromatographed on flash silica eluting with ethyl acetate-cyclohexane mixtures (1:4→4:1). Appropriate fractions were combined and evaporated to give a gum (3.382g). A portion (100mg) of this material, 2,2-diphenylethylamine (62mg) and N,N-diisopropylethylamine (40.5mg) were heated under reflux in isopropanol (7ml) for 18h. The solution was cooled to room temperature, poured into water and extracted with ethyl acetate (2x50ml). The organic extracts were combined, washed with water (50ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown gum (150mg). This was chromatographed on flash silica eluting with ethyl acetate-cyclohexane mixtures (1:1-1:0). Fractions which contained the major component were combined and evaporated to give the title compound as a cream coloured solid (66mg). MH^+ =561; i.r. ($CHBr_3$) ν includes 3420.6, 1616.5cm^{-1} ; ^1H nmr δ ($CDCl_3$) includes 1.18 (t, 3H), 1.31 (s, 3H), 1.56 (s, 3H), 2.45-2.71 (m, 2H), 2.74-2.87 (m, 1H), 3.24-3.41 (m, 2H),

4.25 (bs, fine coupling, 2H), 4.36 (t, 1H), 4.78-5.0 (m, 3H), 5.78 (s, fine coupling, 1H), 5.94 (s, 1H), 7.08-7.41 (m, 10H), 7.77 (s, 1H).

Alternative Preparations of Intermediate 9:

1. (3aR, 4S, 6R, 6aS)-6-(2,6-Dichloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide (85mg) was treated with 2,2-diphenylethylamine (959 mg), N,N-disopropylethylamine (0.053 ml) and propan-2-ol (2.8 ml). The reaction mixture was heated under reflux under nitrogen for 18h. More 2,2-diphenylethylamine (29 mg), N,N-disopropylethylamine (0.026 ml) were added and the reation mixture heated under reflux for a further 10h. The reaction mixture was allowed to cool and the solvent was evaporated under reduced pressure to give a brown foam (174 mg). This foam was purified by column chromatography on flash silica, eluted with methanol-chloroform (0% → 3%) to give the title compound (86mg) whose ^{1}H nmr spectrum ($CDCl_3$) was identical to that of the authentic sample.

2. (3aR,4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid (1 g) was dissolved in dry DMF (10 ml) and treated with triethylamine (0.28 ml). The solution was then cooled to 0 °C while pivaloyl chloride (0.3 ml) was added dropwise with stirring. After the addition was complete the mixture was stirred a further 45 min. at 0 °C. A solution of ethylamine (1 ml) in DMF (4 ml) was then added and the mixture allowed to warm to 21 °C. After 24 h the mixture was diluted with ethyl acetate (150 ml) and washed with 2N HCl (100 ml) followed by saturated sodium hydrogen carbonate solution and finally brine (each 100 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was then purified by flash silica chromatography (eluant 5% methanol in chloroform) to give the title compound as a foam (670 mg) found to be identical to authentic material by ^{1}H nmr.

Intermediate 10

(1S.2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide

(3aR,4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]-dioxole-4-carboxylic acid ethylamide

(300mg) was stirred in trifluoroacetic acid (3.6ml) and water (0.4ml) at room temperature for 1½h. The solution was evaporated under reduced pressure and the residue was evaporated several times from ether to give a cream coloured foam (258mg). This was purified by reverse phase HPLC (30-70% acetonitrile) to give the title compound as a solid (86mg). MH^+=, 521; ^1H nmr δ (CD_3OD) includes 1.14 (t, 3H), 2.07-2.23 (m, 1H), 2.49-2.64 (m, 1H), 2.79-2.91 (m, 1H), 3.24 (q, 2H), 4.16-4.26 (m, 3H), 4.35-4.52 (m, 3H), 7.12-7.36 (m, 10H), 8.24 (s, 1H).

Alternative Preparations of Intermediate 10

1. A solution of (3aR,4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide (250 mg) in acetonitrile (7ml) was treated with 2M hydrochloric acid (12.5ml) The reaction mixture was stirred at room temperature for 1.75h. The solvent was evaporated under reduced pressure and then azeotroped with toluene to give a gum (312mg). This was purified by column chromatography on flash silica, eluted with dichloromethane: methanol: 0.88 aqueous ammonia (30:4:1) to give the title compound as a white foam (226mg) ^1H nmr consistent with authentic sample.

2. (1S, 2R, 3S, 4R)-4-(2-6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentane carboxylic acid ethylamide (144 mg) was treated with 2,2-diphenyl ethylamine (110mg), N,N-disopropyl ethylamine (0.098 ml) and propan-2-ol (6ml). The reaction mixture was heated under reflux under nitrogen for 17h. The reaction mixture was allowed to cool and the solvent was evaporated under reduced pressure to give a white foam (285 mg) which was purified by column chromatography on flash silica, eluted with dichloromethane: methanol: 0.88 aqueous ammonia (30:4:1) and crystallized from methanol to give the title compound as a white solid (149 mg). Its ^1H nmr spectrum (CD_3OD) was identical to that of the authentic sample.

Intermediate 11

(1S, 2R, 3S, 4R)-4-[2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide

Trimethyl orthoformate (8ml) and concentrated hydrochloric acid (0.1ml) was added to (3aR, 4S, 6R, 6aS)-6-(5-Amino-2,6-dichloro-pyrimidin-4-ylamino)-2,2-dimethyl-tetrahydro-cyclopenta [1,3] dioxole-4-carboxylic acid ethylamide (500 mg). The reaction mixture was stirred at room temperature for 4.5h and then the solvent was removed under reduced pressure to give a brown foam. The foam was treated with butan-1-ol (15ml) and heated under reflux under nitrogen for 18h. The reaction mixture was allowed to cool and the solvent was evaporated under reduced pressure to give a gum. A solution of the gum in acetonitrile (25ml) was treated with 2M hydrochloric acid (40ml) and stirred at room temperature for 3h. The solvent was removed under reduced pressure by azeotroping with toluene several times to give a gum (489 mg). This gum was purified by column chromatography on flash silica, eluted with methanol-chloroform (2% → 10%) to give the title compound as a white foam (160 mg). MH^+ measured at 360.062820 C_{13} H_{16} Cl_2 N_5 O_3 requires 360.063020; ^1H nmr δ (CD_3OD) 1.15 (t, 3H), 2.27 (m, 1H), 2.65 (m, 1H), 2.88 (m, 1H), 3.26 (q, 2H), 4.26 (t, 1H), 4.51 (m, 1H), 4.98 (m, 1H), 8.84 (s, 1H).

Intermediate 12

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2-amino-6-oxo-1,6-dihydro-purin-9-yl)-cyclopent-1-yl acetate

Carbocyclic Guanosine[2] (38g) was dissolved in acetonitrile (760 ml). Dimethylaminopyridine (200 mg) was then added and the solution maintained at 20 °C in a water bath. Acetic anhydride (47.5 ml) was then added dropwise over 35 min. with stirring. After 1h the dark solution was treated with methanol (40 ml) and stirred for a further 20 min. Evaporation of the solvent under reduced pressure gave the crude product as an oil. Trituration of this oil with water (200 ml) gave the title compound as a brown solid (41g). MH^+ measured at 408.151909 $C_{17}H_{22}N_5O_7$ requires 408.151923. ^1H nmr δ (DMSO-d6) includes 7.86 (s, 1H), 6.46 (s, 2H), 5.57 (m, 1H), 5.21 (m, 1H), 4.85 (m, 1H), 4.20 (m, 2H), 3.4 (m, 1H), 2.35 (m, 1H), 1.85 (m, 1H), 2.1 (s, 3H), 2.08 (s, 3H), 1.95 (s, 3H).

[2]A.M. Exall et al, J. Chem. Soc., Perkin Trans. I, 1991, 2467.

Intermediate 13

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2-amino-6-chloro-purin-9-yl)-cyclopent-1-yl acetate

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2-amino-6-oxo-1,6-dihydro-purin-9-yl)-cyclopent-1-yl acetate (10g) was suspended in dry acetonitrile (50 ml) and treated with tetraethylammonium chloride (8.15g) giving a clear solution. To this was added N,N-dimethylaniline (3.15 ml). The resulting mixture was stirred while phosphorus oxychloride (13.6 ml) was added dropwise over 15 min. The mixture was then heated to reflux for 10 min. After cooling the solvent was then removed under reduced pressure. The residue was then dissolved in chloroform (200 ml) and washed with cold water (2 x 150 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a gum. This was purified on flash silica eluting with ethyl acetate to give the title compound as a white foam. (6.64g). MH^+ Measured at 426.116532 $C_{17}H_{21}ClN_5O_6$ requires 426.118036. ^1H nmr δ (DMS-d6) includes 8.33 (s, 1H), 6.95 (bs, 2H), 5.59 (dd J 8.5 Hz, 6.0 Hz, 1H), 5.21 (dd J 6.0 Hz, 4.0 Hz, 1H), 4.93 (m, 1H), 4.25 (dd J 11.0 Hz, 6.5 Hz, 1H), 4.15 (dd J 11 Hz, 5.5 Hz, 1H), 2.5 (m, 1H), 2.39 (m, 1H), 2.00 (s, 3H), 2.10 (s, 3H), 1.98 (m, 1H), 1.95 (s, 3H).

Intermediate 14

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2,6-dichloro-purin-9-yl)-cyclopent-1-yl acetate

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2-amino-6-chloro-purin-9-yl)-cyclopent-1-yl acetate (77.23g) was dissolved in dry dichloromethane (2.5 l) and treated with pyridine hydrochloride (42.5g), followed by cupric chloride (1.8g). The resulting green solution was cooled to -15 °C under nitrogen. Tert-butyl nitrite (105ml) was then added dropwise with stirring over 30 min. After the addition was complete the mixture was allowed to warm to 21 °C overnight. After 24 h the mixture was washed with cold water (2 x 200 ml) dried ($MgSO_4$) and treated with a mixture of decolourizing charcoal (5g) and flash silica (25g). Filtration and evaporation under reduced pressure then gave an oil. Trituration with 2-propanol gave the title compound as a buff solid (33.5g). Concentration of the mother liquors gave a second crop (31.1g). MH^+ measured at 445.068132 $C_{17}H_{19}Cl_2N_4O_6$ requires 445.068165; ^1H nmr δ (DMSO-d6)

includes 8.92 (s, 1H), 5.61 (m, 1H), 5.25 (m, 1H), 5.12 (m, 1H), 4.35 - 4.1 (m, 2H), 2.70 - 2.30 (m, 2H), 2.1 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.92 (s, 3H).

Intermediate 15

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-1-yl acetate

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-(2,6-dichloro-purin-9-yl)-cyclopent-1-yl acetate (3.0 g) was dissolved in dry 2-propanol (100 ml) and treated with diphenylethylamine (1.7 g), followed by N,N-diisopropylethylamine (1.77 ml). The resulting mixture was heated to reflux under nitrogen. After 4 h the solvent was removed under reduced pressure and the resultant oil purified on flash silica eluted with ethyl acetate, to give the title compound as a buff foam (2.64g). MH^+ measured at 606.211823 $C_{31}H_{32}ClN_5O_6$ requires 606.211937. ^1H nmr δ (DMSO-d6) includes 8.34 (m, 1H), 8.27 (s, 1H), 7.4 - 7.1 (m, 10H), 5.56 (m, 1H), 5.23 (m, 1H), 4.96 (m, 1H), 4.55 (m, 1H), 4.3 - 3.99 (m, 4H), 2.4 (m, 1H), 2.08 (s, 3H), 2.0 (m, 1H), 2.02 (s, 3H), 1.93 (s, 3H).

Intermediate 16

(1R,2S,3R,5R)-3-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-hydroxymethyl-cyclopentane-1,2-diol

(1S,2R,3R,5R)-2-Acetoxy-3-acetoxymethyl-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-1-yl acetate (900 mg) was dissolved in dry methanol (20 ml) and treated with a solution of 30% sodium methoxide in methanol (30 µl). The resulting mixture was stirred at 21 °C under nitrogen for 1 h. Dowex 50xW acid resin was then added until the mixture was neutral to wet pH paper. Filtration and evaporation under reduced pressure then gave the title compound as a foam (561 mg). MH^+ measured at 480.179916 $C_{25}H_{27}ClN_5O_3$ requires 480.180243. ^1H nmr δ (DMSO-d6) includes 8.18 (s, 1H), 7.4-7.16 (m, 10H), 4.63 (m, 1H), 4.57 (m, 1H), 4.25 (m, 1H), 4.04 (m, 1H), 3.83 (m, 1H), 3.52 - 3.4 (m, 2H), 2.23 (m, 1H), 2.03 (m, 1H), 1.61 (m, 1H).

Intermediate 17

(3aR,4R,6R,6aS)-[6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-yl]-methanol

(1R.2S,3R,5R)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-hydroxymethyl-cyclopentane-1,2-diol (2g) was dissolved in acetone (40 ml) containing para-toluenesulfonic acid (1.7g). 2,2-Dimethoxypropane (7.5 ml) was then added and the resulting mixture stirred at 21 °C for 3 h. The solvent was then removed under reduced pressure and the residue dissolved in ethyl acetate (250 ml). This was washed successively with aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml). The organic layer was then dried ($MgSO_4$) and evaporated to give the title compound as a foam (2.1g). MH^+ measured at 520.211472 $C_{28}H_{31}ClN_5O_3$ requires 520.211543. ^1H nmr δ (DMSO-d6) includes 8.40 (s, 1H), 8.30 (s, 1H), 7.40 - 7.14 (m, 10H), 5.00 - 4.46 (m, 5H), 4.07 (m, 3H), 3.51 (m, 2H), 2.38 - 2.01 (m, 3H), 1.50 (s, 3H), 1.25 (s, 3H).

Intermediate 18

(3aR.4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid

(3aR,4R,6R,6aS)-[6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-yl]-methanol (1.85g) was dissolved in a mixture acetonitrile, carbon tetrachloride, and water (each 19 ml). Sodium periodate (3.4 g) was added and the mixture cooled to 5 °C in a cold water bath. Ruthenium trichloride trihydrate (93.6 mg) was then added and the mixture stirred at 5 °C for 1 h. The reaction mixture was then diluted with ethyl acetate (200 ml) and washed with aqueous sodium bisulfite (100 ml), followed by brine (100 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a dark foam (1.9 g). MH^+ measured at 534.190216 $C_{28}H_{29}ClN_5O_4$ requires 534.190807. ^1H nmr δ (CD_3OD) includes 8.03 (s, 1H), 7.36 - 7.12 (m, 10H), 5.10 (m, 2H), 4.95 - 4.70 (m. 1H), 4.47 (t, J 7.5Hz, 1H), 4.20 (m, 2H), 3.05 (m, 1H), 2.60 (m, 2H), 1.56 (s, 3H), 1.32 (s, 3H).

Example 1

(1S.2R,3S,4R)-4-[trans-2-(4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide

(3aR,4S,6R,6aS)-6-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid ethylamide

(Intermediate 9, 500mg) and trans-1,4-diaminocyclohexane (1.018g) were stirred under nitrogen in anhydrous dimethylsulphoxide (15ml) at 130°C for 24h and the solution was then stood at room temperature for 72h. The mixture was poured into aqueous sodium chloride solution (300ml) and partitioned with ethyl acetate (2x150ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow/brown foam (569mg). This was chromatographed on flash silica eluting with dichloromethane:methanol:880 ammonia solution (30:4:1). Fractions which contained a mixture of a less polar and more polar component were combined and evaporated to give a yellow solid (344mg). This was dissolved in trifluoracetic acid (4.5ml) and water (0.5ml) and stirred at room temperature for 2h. The solvent was evaporated and the residue was evaporated several times from ether to give a yellow/brown foam (617mg). This was purified by column chromatography on flash silica eluting with dichloromethane:methanol:880 ammonia solution (30:6:1).

Fractions which contained the major component were combined and evaporated to give the title compound as a pale yellow amorphous solid (145mg), M/Z 599 (MH^+), ^1H nmr (DMSO-d_6) δ includes 1.03 (t, 3H), 1.25 (m, 5H), 1.71-2.01 (m, 6H), 2.19-2.36 (m, 1H), 2.58-2.74 (m, 2H), 3.10 (m, 2H), 4.06 (m, 2H), 4.23 (m, 1H), 4.43-4.64 (m, 2H), 6.12 (broad, 1H), 7.12-7.39 (m, 10H), 7.78 (s, 1H), 7.92 (t, 1H).

Example 2

Alternative preparation of:
(1S,2R,3S,4R)-4-[trans-2-(4-Amino-cyclohexylamino-6-(2,2-diphenyl-ethylamino-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide

A solution of (1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide (Intermediate 10, 775 mg) in dry dimethyl sulphoxide (23 ml) was treated with 1,4-trans-diaminocyclohexane (1.905g). The reaction mixture was heated under reflux under nitrogen for 5 days. It was allowed to cool and then treated with saturated sodium chloride solution (115ml). This was extracted with ethyl acetate (280ml x 4), dried over magnesium sulphate and the solvent was evaporated under reduced pressure to give an oily residue (2.3g). It was

purified by column chromatography on flash silica eluted with dichloromethane: methanol: 0.88 aqueous ammonia (30:6:1) to give the title compound as a brown foam (334 mg) MH^+ measured at 599.345505 C_{33} H_{43} N_8 O_3 requires 599.345813; ^1H nmr δ (DMSO-d_6) was identical to that of the authentic sample.

Example 3

(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(piperidin-1-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentane carboxylic acid ethylamide

(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide (Intermediate 10, 400 mg) was dissolved in dry dimethylsulfoxide (5 ml). 1-(2-Aminoethyl)-piperidine (1.1 ml) was added and the mixture heated to 126 °C under nitrogen, for 24 h. The cold reaction mixture was diluted with ethyl acetate (150 ml) and extracted with 5% citric acid solution (100ml). This was washed with ethyl acetate (50 ml) then basified with 10% sodium hydroxide solution to pH 8. The aqueous layer was extracted with ethyl acetate (2 x 100 ml) and the combined extracts dried ($MgSO_4$), and evaporated under reduced pressure to give the title compound as a foam (350 mg). ^1H nmr δ ($CDCl_3$) includes 7.43 (s, 1H), 7.36 (m, 10H), 4.55 - 4.1 (m, 6H), 3.55 - 3.25 (m, 4H), 2.85 (m, 1H), 2.77 - 2.32 (m, 8H), 1.66 - 1.36 (m, 6H), 1.18 (t, 7 Hz, 3H).

Example 4

(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide

A suspension of 1-methyl histamine (198mg) dihydrochloride in dry methanol was treated with a solution of sodium hydroxide in dry methanol (1.7ml of a 25ml solution containing 1.1g NaOH). After stirring at 21°C for 15min. the solvent was removed under reduced pressure and the residue dissolved in dimethylsulphoxide (2ml). To this was then added (1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclo-pentanecarboxylic acid ethylamide (Intermediate 10, 120mg) and the resulting mixture heated to 130°C under nitrogen. After 48h the mixture was allowed to cool and diluted with ethyl acetate (100ml). This was washed with brine (3x 25ml) and the combined aqueous layers back-extracted with ethyl acetate (25ml). The

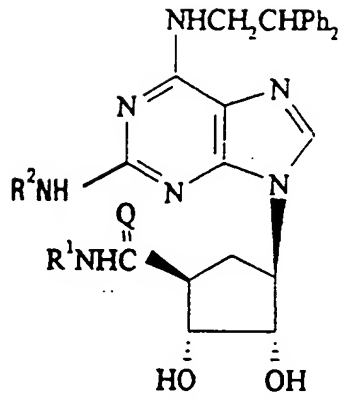
combined extracts were dried and evaporated to give a black tar. This was purified by preparative thin layer TLC (dichloromethane, ethanol, 880-ammonia, 100/8/1) to give the title compound (46mg) as a foam. MH^+ = 610, 1H nmr δ (CD_3OD) includes 7.80 (s,1H), 7.48(s, 1H), 7.35-7.14 (m, 10H), 6.76 (s, 1H), 4.66(m, 1H), 4.55-4.30 (m, 4H), 4.18 (m, 3H), 3.64 (s, 3H), 3.23 (q, 2H), 2.82(m, 3H), 2.50 (m, 1H), 2.22 (m,1H), 1.14 (t, 3H).

The effects of compounds of the invention on fMLP activation of O_2^- generation

The potential for compounds of formula (I) to inhibit leukocyte function was examined by measuring the ability of the compounds to inhibit superoxide (O_2^-) generation from neutrophils stimulated with fMLP following the procedure described by W. Busse et al. in J. Allergy Clin. Immunology, 83(2) Part 1, 400-405 (1989). Thus, compounds of Examples 1 to 4 were at least four fold more active than NECA in this study. Indeed, the compound of Example 4 is 50 times more potent than NECA in this study.

CLAIMS

1. A compound of formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-8}cycloalkyl or C_{1-6}alkyl group;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

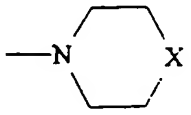
(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) -Alk_1Y where Alk_1 is a C_{2-6} alkylene group and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl) and

(viii) -$(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, carboxyC_{1-4}alkyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl.

2. A compound according to Claim 1 in which R^1 is C_{1-3} alkyl.

3. A compound according to Claim 1 or Claim 2 in which Q is an oxygen atom.

4. A compound according to Claim 1 in which $R^1NHC(=Q)$- is ethylaminocarbonyl.

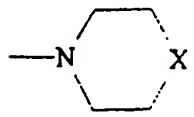
5. A compound according to any preceding claim in which R^2 is cyclopentyl or cyclohexyl each substituted by one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido.

6. A compound according to any of Claims 1 to 4 in which R^2 is pyrrolidin-3-yl or piperidin-3-yl in which the respective rings may each be substituted by hydrogen, C_{1-3} alkyl or benzyl.

7. A compound according to any of Claims 1 to 4 in which R^2 is $-(CHR^5)m(Alk_2)_nZ$ in which Z is an optionally substituted imidazolyl group.

8. A compound according to Claim 7 in which $-(CHR^5)m(Alk_2)_n-$ is $-CH_2CH_2-$.

9. A compound according to any of Claims 1 to 4 in which R^2 is Alk_1Y where Alk_1 is a C_2 alkylene group and Y is



(where X is a bond, O, CH_2).

10. (1S,2R,3S,4R)-4-[trans-2-(4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide;
(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(piperidin-1-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentane carboxylic acid ethylamide;
(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid ethylamide;
and physiologically acceptable salts and solvates thereof.

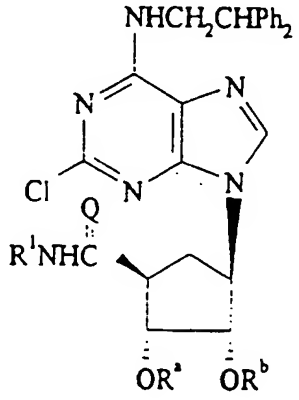
11. A compound of formula (I) as defined in any preceding claim for use in human or veterinary medicine.

12. Use of a compound of formula (I) as defined in any of Claims 1 to 10 for the manufacture of a medicament for the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

13. A pharmaceutical composition comprising a compound of formula (I) as defined in any of Claims 1 to 10 together, if desirable, with one or more physiologically acceptable carriers or excipients.

14. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises;

(A) treating a compound of formula (II)



(II)

(wherein R^a and R^b each represent a hydrogen atom or together form an alkylidene group such as isopropylidene) with an amine $R^{2a}NH_2$ (wherein R^{2a} is a group R^2 or a protected derivative thereof), followed, where necessary, by the removal of any protecting groups present; or

(B) deprotecting a protected derivative of a compound of formula (I), if necessary or desirable followed by (I) salt formation or (II) conversion of a compound of formula (I) to a different compound of formula (I) or (III) preparation of an individual isomer of a compound of formula (I).

15. A method for the treatment of a human or animal subject with an inflammatory condition which is susceptible to leukocyte-induced tissue damage, which method comprises administering to said subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

16. Compounds according to any of Claims 1 to 10 substantially as herein described.

17. Compositions according to Claim 13 substantially as herein described.

18. A process for the preparation of a compound according to Claim 1, the process substantially as herein described and exemplified.

Inter... Application No
PCT/EP 95/02705

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 039 689 (SUSAN M. DALUGE) 13 August 1991 *Document* ---	1-18
A	WO,A,92 05177 (RHONE-POULENC RORER INTERNATIONAL INC.) 2 April 1992 *Pages 56-61: claims* ---	1-18
A	EP,A,0 368 640 (THE WELLCOME FOUNDATION LIMITED) 16 May 1990 *Page 18-20: claims* ---	1-18
A	EP,A,0 431 799 (THE WELLCOME FOUNDATION) 12 June 1991 *Page 13-15: claims* ---	1-18
A	EP,A,0 267 878 (CIBA-GEIGY AG) 18 May 1988 *Page 19-24: claims* --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search
28 November 1995

Date of mailing of the international search report
1. 12. 95

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C.(Continuation) DOCUM.. IS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON LETTERS, vol.30, no.41, 1989 pages 5543 - 5546 JEN CHEN ET AL *Page 5545* ---	1-18
P,A	JOURNAL OF MEDICINAL CHEMISTRY, vol.38, no.7, March 1995 pages 1174 - 1188 SUHAIB M SIDDIQI ET AL *Page 1180: table 1, compound 44* *Page 1181* -----	1-18

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INTEF TIONAL SEARCH REPORT

International application No.
PCT/EP 95/02705

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compounds/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5039689	13-08-91	NONE		
WO-A-9205177	02-04-92	AU-B-	654507	10-11-94
		AU-B-	8726691	15-04-92
		CA-A-	2092305	26-03-92
		EP-A-	0550631	14-07-93
		US-A-	5217982	08-06-93
		US-A-	5364862	15-11-94
EP-A-0368640	16-05-90	JP-A-	2237981	20-09-90
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		AU-B-	8119387	19-05-88
		CA-A-	1288431	03-09-91
		JP-A-	63135384	07-06-88
		US-A-	4954504	04-09-90
		US-A-	5063233	05-11-91
		ZA-A-	8708527	16-05-88